REMARKS

Applicants have amended claims 8, 9, 13, 14, and 15 to correct the form of the claims from using "and" to using "or."

Applicants have amended claim 17 to correct the dependency to provide antecedent basis for the claim.

Accordingly, the amendments are clerical and do not introduce new matter and their entry is respectfully requested.

Applicants have added new claims 18, 19, and 20.

Support for claim 18 can be found throughout the specification, for example, at page 9, second full paragraph.

Support for claim 19 can be found throughout the specification, for example in the paragraph bridging pages 8 and 9, and page 21, last full paragraph.

Claim 20 is supported throughout the specification and is a specific embodiment of claim 3.

Accordingly, the new claims do not introduce new matter and their entry is respectfully requested.

Turning now to the specific rejections.

The Examiner maintained the rejection of claims 1, 3-5, and 5-17 as being unpatentable under 35 U.S.C. 103 over Beug et al., Chaudhary et al. and Wu et al.

Applicants respectfully disagree.

The claimed specific nucleic acid delivery system and the method of using the system provide a significant, and unexpected improvement over the nucleic acid delivery methods that were known and used at the time of filing this application.

The claimed nucleic acid delivery system can efficiently deliver nucleic acids, such as RNA, *in vivo*. This is because one can prepare in a simple manned a fusion protein and select those cells expressing fusion proteins that have better binding activity and use such cells to reproducibly prepare the fusion proteins that have the desired binding and targeting activity (see, e.g., Examples beginning at page 24 of the specification, where a fusion protein is first constructed and then tested for targeting and nucleic acid binding). This is entirely different than the chemical conjugate where every time one produces a new conjugate from a mixture of ingredients it is a hit or miss prospect what type of delivery system is made.

More specifically, as explained in the Amendment dated March 17, 2006, the specification

teaches, for example, at page 23, second full paragraph, that the construct of the present invention provides a superior delivery method compared to prior art - one that can be efficiently produced and provide high binding activity.

Further, the last paragraph of page 38 continuing into and through page 39, discusses the reasons why this method provides a more efficient delivery system as compared to prior art, such as Wu. For example, when discussing the advantages of the present system for delivering a desired product to the cells, the specification reads "[f]urthermore, the bifunctional recombinant fusion proteins as a gene carrier also have the advantage over chemically linked ones [**citing references including Wu**], such as efficient production, and potentially better binding activity" (page 39, emphasis added).

Neither Chaudhary nor Beug provide any evidence why delivery of nucleic acids using a fusion protein of the present invention would be superior to Wu, whereas the present application clearly describes the benefits provided by this system over, e.g. Wu. The better binding activity and consequently improved delivery of nucleic acids using the claimed system and methods have been shown, with particularly striking results as discussed in the already submitted documents including Song et al. submitted with the Amendment dated June 6, 2005, and the editorial by Rossi submitted with the Amendment dated March 17, 2006, all confirm this teaching.

The Examiner argued, that the citation to "potentially better binding activity" would be recognized by the skilled artisan to indicate "that the activity of the resulting protein would depend on various factors for making fusion proteins as well as the inherent problems/properties of the fusion protein itself." However, the Examiner ignores the expert declaration of Dr. Marasco, a skilled artisan, who was aware of the problems of chemical conjugates, such as those produced by Wu, and specifically stated that "[g]iven the challenges to cloning at the time, as reflected in Chaudhary, it would not have been obvious to the typical researcher in this field at the time to adopt Wu's system to create a fusion protein. Indeed, it would be taught against, since Wu taught that it was beneficial that the covalent bond could be cleaved in the cell whereas a peptide bond is not readily cleaved (Col. 5, lines 37-48)"(see, e.g., paragraph 11 of the Declaration).

The Examiner also contended that the problems described by Rossi in the nucleic acid delivery systems are not on point because Rossi relates to delivery of naked RNA. However, the present system is designed precisely for that purpose, namely, delivery to specific target cells of naked nucleic acids, such as RNA. Thus the problems discussed in Rossi are highly relevant. The present invention provides a method by which naked nucleic acids, such as RNA can be delivered both *in vitro* and *in vivo* to desired

cells with significantly increased efficiency, including efficient targeting and intracellular delivery, when compared to other methods available to one skilled in the art at the time of filing the application.

Unlike the chemical conjugates proposed by Wu, the claimed system and methods provide a significant improvement in efficiency of production because upon selecting a desired fusion protein one knows what the subsequent fusion protein will be and knows that the fusion molecules having produced are active. Thus, when nucleic acid is combined with the fusion protein, each fusion protein is correctly folded and capable of binding nucleic acids. Whereas the fusion proteins produced by the methods of Wu, are a hit or miss proposition wherein incorrectly fused conjugates or otherwise conjugates with low targeting or nucleic acid binding properties are likely to be present, because they are produced using two separate molecules and chemical conjugation method. Wu does not teach how to select and separate the fusion proteins with correct conformation or binding or targeting capacity from the ones that have incorrect conformation or inefficient delivery or nucleic acid binding proterties. Thus, one uses a mixture containing many inefficient fused proteins. Using such mixtures results in inefficiency in targeting and reduction in binding of nucleic acids when compared to the fusion proteins of the present invention, where reproducibility is built in to the system. This is also evidenced by the much better efficiency of delivery of nucleic acids, such as RNA.

Although the Examiner contends that Wu teaches delivery of RNA, Applicants submit that Examiner reads into Wu something that is simply not there. The only place where RNA is mentioned in Wu, is a prior art citation to "Weiner et al. "Development of molecular hybridization technology to evoluate albumin and procollagen in mRNA content in baboons and man," Chemical Abstracts, vol. 106, pp. 338, Ref. #152326f, 1987." Nothing in Wu teaches or suggests that RNA can be delivered using even the method of Wu. Neither Chaudhary nor Beug cure this defect in Wu.

Accordingly, Applicants submit that the cited prior art does not teach all the elements of the claims directed to system and methods of delivering RNA, such as required by claims 17-19.

Applicants maintain, that neither Wu, nor Chaudhary or Beug teach the benefits of using antibody as a targeting moiety. Certainly, none of the cited references teach using an antibody against a viral envelope protein to target cells, as required by claim 20.

Claim 6 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Beug et al. in view of Chaudhary et al. and Wu et al as applied to Claims 1, 3 – 5, and 7 – 16, and further in view of Ryder et al.

Applicants disagree for the reasons in record and incorporated herein by references. However, to expedite prosecution, Applicants have cancelled claim 6.

In view of the foregoing arguments and amended claims, Applicants respectfully submit that claims 1, 3-5, 7-17 comply with both 35 U.S.C. §103(a).

At minimum, claims 17, 18 and 19 directed to delivery of RNA, and claim 20 directed specifically to a use of an antibody against a viral envelope protein, should be in condition of allowance.

In view of the foregoing, applicants respectfully submit all claims are in condition for allowance. Early and favourable action is requested.

Respectfully submitted,

Date: 8/31/06

Ronald I. Eisenstein (Reg. No.: 30,628)
Leena H. Karttunen (L0207)
NIXON PEABODY LLP
100 Summer Street
Boston, MA 02110
(617) 345-6054